

Separately tackling the development of erosions with denosumab: ultimately closing a gap in the treatment of patients with rheumatoid arthritis or trying too hard too late?

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Patients with rheumatoid arthritis (RA) have benefited from an unprecedented treatment improvement over the last two decades. Taking the disease seriously, with earlier and more intensive treat-to-target strategies and new treatment options with biologicals, has led to a better long-term disease control. Classical antirheumatic therapies, primarily directed against the inflammatory/immunological processes that determine RA disease activity, are successfully improving pain and the severe clinical and functional burden patients are confronted with. Moreover, one of the most important previous hallmarks of this disease, severe joint destruction with subsequent deformations, can now in most cases be prevented thanks to the development of new treatment strategies and the introduction of novel therapeutics. The Cobra trial¹ demonstrated the existence of a window of opportunity for preventing joint damage in early RA and the Attract trial² showed an arrest in further X-ray damage—at least at the group level—in severe methotrexate (MTX) refractory disease treated with infliximab, which was unprecedented at that time. Thanks to more effective treatments prevention of further damage was reported and even, in a (small) number of cases, what could be considered as healing of erosions.^{3, 4} Other publications focused on a potential uncoupling between controlling inflammation and damage. Prevention of X-ray progression appeared possible independent from successfully reducing disease activity, at least with certain therapeutics.⁵ Despite the fact that today joint damage can be prevented in the large majority of cases, it is still an important determinant in the

evaluation of RA treatment efficacy given the link between X-ray progression and future physical disability.⁶

Takeuchi *et al*⁷ demonstrate an additional inhibitory effect on the progression of bone erosions (not joint space narrowing) of three different dosages of denosumab on top of the traditional RA treatment over a 12-month period in Japanese patients with RA, confirming results reported already 8 years ago by Cohen *et al*⁸ in North America. Although the erosive changes are relatively small and a certain ‘hang-over’ of MTX is possible, this study has clear strengths like the placebo-controlled design, the relatively early study population, the similar evolution of disease activity markers across treatment arms and the documentation of improved bone-turnover and not cartilage-turnover markers, confirming the X-ray results. The results are convincing even though the study population consisted of patients with relatively low disease activity. One wonders what this would have been in more active patients or with less glucocorticoid use. On the other hand, the treat-to-target approach was not applied, making the relevance of the study results for daily practice somewhat uncertain. Nevertheless, this study confirms the predefined proof of concept that denosumab can be of help in preventing joint erosions in RA.

Earlier attempts to prevent (cartilage) damage in RA with therapeutic agents not specifically targeting joint inflammation were already initiated >15 years ago, focusing mainly on metalloproteinase inhibitors. A nice overview on this topic was written by Close⁹ in this journal in 2001. Questions about representativeness of the animal models the drugs were tested in, lack of sensitivity in outcome measurements, and specificity and safety issues of the drugs tested, were raised. Inefficacy of minocycline—known also for its collagenase inhibitory properties—in preventing X-ray damage in RA¹⁰ and the preliminary discontinuation of the

Trocade trial with a MMP-1 inhibitor despite promising explorative findings,¹¹ precluded further research along this therapeutic pathway in RA because of an apparent unfavourable risk–benefit profile. Currently, matrix metalloproteinase-3 is still under investigation although not so much as a direct therapeutic target but rather as a predictive biomarker for joint damage and therefore as an additional measurement instrument in treat-to-target strategies.^{12, 13} In the meantime, attempts to separately tackle bony erosions were continued at a smaller scale and with mixed success, with denosumab and with bisphosphonates¹⁴ and parathormone (PTH),¹⁵ but apparently without real breakthrough and without any further implementation in daily practice.

While the idea of additional prevention of cartilage and/or bone destruction with agents not directly targeting inflammation is being investigated already for more than two decades and is again brought to our attention with this denosumab trial, one could question the relevance of this complementary approach given the successfulness of current RA treatment standards.

There is no doubt that avoiding the occurrence of joint erosions is still an important issue. Joint erosions historically have always been perceived to be a critical indicator of permanent future disability in patients with RA, although data suggest also that joint space narrowing, occurring early in disease process, may be a more important determinant of irreversible physical disability.^{6, 16} On the other hand, erosions are more prevalent than joint space narrowing in early RA and a recent study suggested existing erosions in a single joint are associated with future joint space narrowing making it clear that tackling both bone and cartilage damage is important, especially in early disease. Interestingly, these data derived from the PREMIER study¹⁷ also suggested that the effect of pre-existing erosions on future joint space narrowing, documented in the MTX+adalimumab (ADA) and the ADA monotherapy group, was at least partly independent from the presence of clinical synovitis.

Thanks to the availability of effective therapeutic strategies we are more successful in controlling disease activity than ever before, but we should not forget to evaluate joint damage as an objective and cumulative readout of treatment effectiveness. Swollen joint counts and all disease activity measurement instruments including swollen joints, as well as acute phase reactants, are still robustly associated with radiographic damage.¹⁸ This highlights

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the importance of the ongoing discussion about the definition of 'real remission' and how to evaluate this in daily practice¹⁹ as well as further research on how to implement effective intensive treatment strategies as quickly as possible, especially in early disease.²⁰

Perhaps not surprisingly, in trials with the more recently developed tumour necrosis factor blockers like golimumab it appeared more difficult to demonstrate a significant radiographic benefit from the study drug because X-ray progression in the so-called MTX-refractory study population was globally lower than expected.²¹ The latter findings led to an important viewpoint paper by Landewé *et al*²² focusing on trial design and statistical challenges when evaluating patients with RA and measuring treatment efficacy, especially efficacy based on X-ray outcomes. Dr Landewé correctly states that we can no longer hang on to the classical enrichment techniques selecting very active patients with a severe risk profile for inclusion in trials, with the aim of demonstrating superiority in damage control of one treatment over another, without serious ethical problems in an era where many effective alternative therapies are available. He proposes to replace 'inhibition of radiographic progression' by 'maintaining structural integrity' as an outcome parameter in clinical trials. While the focus of this paper was on methodological issues as a consequence of the limited radiographic progression in clinical trials, this seems perfectly in accordance with our own experiences in daily practice, where early intensive step down and treat-to-target strategies are capable of bringing RA disease activity under control in the vast majority of patients, making X-ray damage little by little a minor problem.²³ For the subset of patients refractory to optimal initial treatment, today several additional treatments are available to control disease activity and in this way avoid radiographic progression.

In view of preventing radiographic damage and future disability it is clear that aspects of timely treatment and avoiding treatment delay,²⁴ as well as personalised communication with individual patients about their fears and beliefs, and issues related to the implementation of early intensive treatments in daily practice^{25 26} are at least as important as the introduction of new and sophisticated medication. Some of us might still tend to adapt their treatment choices based on markers of a bad prognosis in terms of future X-ray damage. Unfortunately

however, current prediction matrices combining several of these markers in order to improve their predictive capacity still do not perform adequately when used in daily practice²⁷ probably as a consequence of the growing application, although flexibly, of the treat-to-target principle. From our point of view, pending the discovery of more adequate prognostic biomarkers allowing personalised treatment stratification, all patients with RA should be treated intensively and any symptoms and signs pointing to remaining disease activity should be taken seriously, irrespective of the patient's traditional risk profile. We agree with the mantra of 'maintaining structural integrity' also in the present treatment era, but would like to expand this towards 'for as many patients as possible' and hopefully allowing 'maintenance of optimal societal participation'.

A last and very important issue to consider is the eventual additional cost for the introduction of denosumab as an adjuvant therapy for RA in an era where societal expenditures for biologicals are already very high and even utopic in many countries of our world. It is questionable if cost-effectivity would ever be reached taking into consideration the treatment goals already achieved using the present armamentarium. Probably, for most patients a more adequate implementation of the current knowledge on how to induce and maintain disease control would be more cost-effective than trying to tackle additionally the progression of erosions with denosumab. Of course besides improving inflammation and preventing joint damage, adequate RA management involves also the prevention and treatment of associated co-morbidities and safety issues that might occur with any additional therapy. The proposed additional denosumab treatment could, apart from preventing joint erosions, in certain patients also constitute a therapy for RA-associated osteoporosis, as suggested in the current paper⁷ reporting also increased bone density. One could therefore consider to reserve such therapy for those patients with RA with a particularly high fracture risk, in order to improve the cost-effectiveness.

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